REMARKS

Status of Application

Claims 1-2 are pending and claims 3-7 are withdrawn from consideration. Applicant reserves the right to prosecute any withdrawn, canceled, or non-elected claims and/or subject matter in separate application(s).

Applicant requests reconsideration and allowance of claims 1 and 2, and allowance and rejoinder of withdrawn claims 3-4.

35 U.S.C. § 112 Rejection

Applicant herein amended claim 1 to clarify the units of sodium chloride. Thus, this rejection is obviated.

35 U.S.C. § 103 Rejections

Examiner rejected claims 1-2 as obvious over APC (EP 0 115 627) (hereinafter, "EP '627") in combination with Azria et al. (U.S. Patent No. 5,759,565) (hereinafter, "the '565 patent"). Examiner stated that Azria teaches a calcitonin solution and that "Chlorobutanol is also taught as being use in the nasal composition but suffers from some drawbacks when used at 0.6%." Examiner further stated that "Azria et al. does not teach the use of Chlorobutanol at ranges lower than that of 0.6%." Because Applicant's composition of claims 1-2 contains chlorobutanol at a concentration of 0.25% (w/w), Examiner therefore turned to EP '627 and stated that EP '627 teaches "the use of Chlorobutanol (a preservative) in the range of 0.001-2.0 %(w/v)." Examiner concluded that it would have been obvious to optimize the concentration of chlorobutanol, and that it would have been obvious to optimize the components in EP '627 and Azria et al. Examiner further stated that "[o]ne would have been motivated to modify the composition as taught by both APC and Azria et al. to optimize the concentration parameters" and "[f]rom the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention."

Applicant responds that Examiner has not supplied a *prima facie* case for obviousness because Azria et al. teach away from use of chlorobutanol in a calcitonin solution. Applicant respectfully submits that Examiner *wrongly concluded* that Azria et al. teach the use of

chlorobutanol in a calcitonin solution. To the contrary, the language of Azria et al. plainly and unambiguously teaches away from using chlorobutanol in a calcitonin solution. ('565 patent, col. 2, lines 35-61) Azria et al. state that chlorobutanol is not suitable for use in a calcitonin nasal spray because experimental results showed that at a concentration of 0.6% chlorobutanol "showed insufficient activity against the test fungus *Pen. Steckii,* more than 3 days being required to reduce the cell count to less than 0.1%." These statements plainly mean that chlorobutanol did not have sufficient activity as a preservative to be suitable for use in a calcitonin nasal spray. In other words, Azria et al. provide the *specific evidence* that chlorobutanol at a concentration of 0.6% is not suitable for use in a calcitonin nasal spray. Azria et al. also provide an explanation for the insufficient activity of a preservative. ('565 patent, col. 2, lines 17-20) In view of this specific and credible evidence, Examiner must conclude that Azria et al. teaches away from using chlorobutanol in a calcitonin nasal spray.

Further, Azria et al. give other evidence that chlorobutanol is not suitable for use in a calcitonin nasal spray. In particular, chlorobutanol "was found to attack rubber stoppers and other joints used in nasal spray applicators." ('565 patent, col. 2, lines 35-61) Azria et al. do not state that there is a limiting concentration for this disadvantage, and state that it is a concern because the pharmaceutical composition may be "stored for months before use" and dosing "may extend over a period of several days or weeks." ('565 patent, col. 2, lines 15 and 22) Importantly, Azria et al. refer back to this disadvantage in stating that their invention is "eminently suitable for use in multiple dose nasal spray appplicators" because it contains an alternative to chlorobutanol, namely benzalkonium chloride. ('565 patent, col. 2, lines 56-57)

Moreover, Azria et al. state that chlorobutanol has other disadvantages including that it caused "inhibition of the ciliary beating frequency of rat trachea." ('565 patent, col. 2, lines 46-51)

In sum, Examiner has wrongly ignored the plain and unambiguous teaching of Azria et al. that chlorobutanol was not considered suitable for use in a calcitonin nasal spray. Undeniably, the teachings of Azria et al. would have strongly dissuaded a person of ordinary skill in the art from using chlorobutanol in a calcitonin nasal spray, and would have led the artisan to use the alternative benzalkonium chloride. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from

following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the Applicant." *Optivus Techn., Inc. v. Loma Linda Univ. Med. Center*, 80 U.S.P.Q.2d 1839, 1848 (Fed. Cir. 2006).

Applicant respectfully submits that Examiner must point to evidence in the references and that Examiner's statement that "one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention" is a conclusory recitation of a rule without any support.

Examiner has not supplied a *prima facie* case for obviousness because the fact that Azria et al. teach away from use of chlorobutanol in a calcitonin nasal spray means that a person of ordinary skill in the art would not have been motivated to look to the EP '627 or any other reference for use of chlorobutanol. The plain and unambiguous teaching of Azria et al. that chlorobutanol has insufficient activity as a preservative would only have motivated a person of ordinary skill in the art to have removed or replaced chlorobutanol, or in other words to have used an alternative, suitable preservative.

Examiner's suggested combination of Azria et al. with the EP '627 does not supply a *prima facie* case for obviousness because EP '627 does not supply evidence that chlorobutanol is suitable in a calcitonin solution. Examiner points to the disclosure in EP '627 of "Preservatives" in the range 0.001 to 2.0 % (w/v). (EP '627, page 6, line 21) This general disclosure, without guidance, does not make obvious the use of any particular preservative. In fact, EP ′627 merely lists chlorobutanol at a concentration of 0.5-1.0 % (w/v) and 0.1 % (w/v) in generalized example compositions. (EP '627, page 7, line 6, and page 10, line 19) But EP '627 provides no evidence that the disclosed compositions have or maintain reduced levels of fungus or microorganisms which a preservative must do. Therefore, Examiner must accept the evidence of Azria et al., which was published after the EP '627 was published, and showed that chlorobutanol is not suitable in a calcitonin solution. To a person of ordinary skill in the art at the time of Applicant's invention, Azria et al. directly contradicted any implication of the EP '627 that chlorobutanol might be suitable. Therefore, the plain and unambiguous evidence of Azria et al. that chlorobutanol had insufficient activity as a preservative in a calcitonin solution would have overruled any implication of EP ′627 that chlorobutanol was suitable. Examiner has not supplied a *prima facie* case for obviousness because a person of ordinary skill in the art at the time of

Applicant's invention would not have been motivated to look back to the earlier EP '627 for mere disclosure of chlorobutanol as a preservative when its use was directly contradicted by factual evidence from a standard test in Azria et al.

Examiner appears to propose that a general motivation to achieve Applicant's invention would have been found in the need to optimize and vary the concentrations of the components of a combination. However, varying concentration parameters without guidance is an improper "obvious to try" standard for patentability. (M.P.E.P 2145, Part X) Moreover, Applicant respectfully submits that the proposal to optimize the concentration of chlorobutanol in a calcitonin nasal spray should be considered a teaching away from Applicant's claim 1-2 because the factual evidence provided in Azria et al. was that concentrations lower than 0.6% were insufficient against test fungus. This fact means that no amount of experimental optimization would have assisted a person of ordinary skill in the art to achieve Applicant's invention because the fact Examiner must accept is that concentrations lower than 0.6% would have been insufficient against test fungus. At the time of Applicant's invention of claims 1-2, the motivation to optimize the concentration of chlorobutanol in a calcitonin solution, as guided by the unambiguous facts in Azria et al., would have been that if chlorobutanol were to be used at all, concentrations much higher than 0.6% would have had to be used. Even if, *arguendo*, a suitable high concentration of chlorobutanol could have been found, this would not have led to Applicant's invention of claims 1-2 which describe chlorobutanol at a concentration of 0.25 % (w/w). Therefore, Examiner's proposal that a general motivation would have been found in the need to optimize concentrations should not be considered motivation to achieve Applicant's invention. Instead, it should properly be viewed as a teaching away. See e.g., *In re Zurko*, 258 F.3d 1379, 1386 (Fed. Cir. 2001) (holding that general conclusions concerning what is "basic knowledge" or "common sense" to one of ordinary skill in the art without specific factual findings and some concrete evidence in the record to support these findings will not support an obviousness rejection).

In another aspect, Examiner has not supplied a *prima facie* case for obviousness because neither Azria et al. nor EP '627 disclose or suggest a calcitonin nasal spray solution containing less than 5% oxygen as claimed by Applicant. Applicant respectfully submits that Examiner cannot ignore this limitation and must show evidence that the cited references make obvious

Applicant's invention as a whole, including each and every claimed limitation. "[M]ere identification in the prior art of each component of a composition does not show that the combination as a whole lacks the necessary attributes for patentability." *Eli Lilly and Co. v. Zenith Goldline Pharms, Inc.*, 81 U.S.P.Q.2d 1324, 1331 (Fed. Cir. 2006) (citing *Kahn*, 441 F.3d at 986 (Fed. Cir. 2006)). Examiner has not pointed to evidence in the references establishing the obviousness of a calcitonin nasal spray containing less than 5% oxygen.

Applicant submits that Azria et al. and EP '627 do not establish a *prima facie* case for obviousness of Applicant's calcitonin nasal spray containing less than 5% oxygen. Neither Azria et al. nor EP '627 discloses the desirability of removing oxygen from a calcitonin solution. To the contrary, Azria et al. disclose that a calcitonin solution can be stored under nitrogen atmosphere. ('565 patent, col. 7, lines 34-37) And EP '627 discloses the use of antioxidants. (EP '627, page 6, line 22) Neither reference teaches degassing the calcitonin solution or any other method to remove oxygen. Rather, these references both teach to leave the oxygen in the calcitonin solution and offer ways to compensate for high levels of oxygen. Therefore, Azria et al. and EP '627 do not fairly teach or imply, either alone or in combination, the motivation to remove the oxygen from a calcitonin solution to achieve Applicant's invention. Examiner proposes, without pointing to specific portions of the references, that a person of ordinary skill in the art in general would have known that the solution could have been degassed. However, general knowledge of a possibility does not suggest the desirability of degassing. Further, as discussed above, both Azria et al. and EP '627 teach alternatives to degassing. Therefore, both Azria et al. and EP '627 teach a preference to leave high levels of oxygen in a calcitonin solution, and do not teach a calcitonin solution containing less than 5% oxygen as claimed by Applicant.

Applicant respectfully requests reconsideration and allowance of claims 1 and 2 and allowance and rejoinder of withdrawn claims 3 and 4. Claims 3 and 4 encompass the use of the compositions of claims 1 and 2, respectively.

It is believed that no fee is required for this submission. Should, however, the U.S. Patent and Trademark Office determine that any fee is due or that a refund is owed for this application, the Commissioner is hereby authorized and requested to charge the required fee and/or credit the refund owed to our Deposit Account No. 502769.

Should there remain any unresolved issue that would require an adverse action, it is respectfully requested that Examiner telephone Applicant's attorney so that such issue may be resolved as expeditiously as possible.

Respectfully submitted,

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